REMARKS

Claims 43-58 are cancelled, and new claims 65-70 are added. Therefore, claims 59-70 are pending. Support for the new claims can be found in the application and claims as filed. For example, cancelled claims 43-58 provide support for new claims 65-70.

The Examiner rejected the claims under 35 U.S.C. §112, 1st paragraph. The Examiner asserts that there is "no working example" or "sufficient guidance" of "treating a human subject afflicted with supraventricular tachyarrhythmia or tachyarrhythmia in a human subject, comprising administering to the human subject a therapeutically effective amount of JTV-519." (See Office Action of Oct. 30, 2007, page 5, ll. 5-10.) The Examiner states that there is "no sufficient evidence showing that human supraventricular tachyarrhythmia is caused by the PKA phosphorylation-induced dissociation of FKBP12.6 from RyR2." Thus, the Office Action concludes that "it would take a large quantity of experimentation to determine whether the PKA phosphorylation-induced dissociation of FKBP12.6 from RyR2 is the cause of human supraventricular tachyarrhythmia ..." and "it is unpredictable whether JTV-519 can be used to treat supraventricular tachyarrhythmia ... [t]herefore, it would require undue experimentation for one skilled in the art to make and use the claimed invention." (See Office Action of Oct. 30, 2007, page 5, l. 11 to page 6.) Applicants respectfully traverse this rejection for the reasons below.

First, applicants respectfully point out that the Examiner has previously agreed that the specification provides enablement for methods of treatment using JTV. More specifically, in the office action mailed on February 16, 2007, the Examiner stated that "the specification ... [is] enabling for a method for treating atrial tachyarrhythmia or inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the human subject a therapeutically effective amount of JTV-519" (Office Action February 16, 2007, page 2). As atrial tachyarrhythmia encompasses supraventricular tachyarrhythmia, the Examiner has acknowledged that the specification is enabling for treating supraventricular tachyarrhythmia . Accordingly, the applicants respectfully request withdrawal of this rejection.

Moreover, independent of the above, Applicants respectfully point out that actual reduction to practice prior to filing is not a requirement for enablement. *See* Gould v. Quigg, 822

F.2d 1074, 1078 (Fed. Cir. 1987). Further, with respect to a method of treatment, a working example can be an *in vitro* model or an *in vivo* animal model if the model shows sufficient correlation to the claimed method of use:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. ... In this regard, the issue "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.

(See MPEP § 2164.02 Working Example – 2100 Patentability.) The instant specification provides a number of *in vitro* and *in vivo* animal model assays that show a strong correlation between altered RyR2 channel function and ventricular arrhythmias. More specifically, the specification shows that defective channel function can be due to depletion of FKBP12.6 from the RyR2 complex, which depletion can be due to PKA-hyperphosphorylation of RyR2. Thus, by showing that JTV-519 promotes FKBP12.6 binding to PKA-hyperphosphorylated RyR2, the specification provides a sufficient basis to pursue administration of JTV-519 to humans for the treatment or inhibition of the onset of supraventricular tachyarrhythmia. This shall be discussed in detail below.

For example, the specification at "Experimental Set II" teaches that there is a relationship between altered RyR2 channel function and arrhythmias. Experimental Set II draws data not only from human patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), but also from the FKBP12.6-deficient mouse animal model:

> The following experiments demonstrate that during exercise, PKA phosphorylation of RyR2 partially dissociates FKBP12.6 from the channel, increasing intracellular Ca^{2+} release and cardiac contractility. Data are provided to show that RyR2 channels from FKBP12.6-deficient mice and from patients with CPVT are more active during exercise compared to controls, and that cardiomyocytes from FKBP12.6-deficient mice exhibit after-depolarizations that can trigger arrhythmias that cause sudden

> cardiac death. New therapeutic approaches for treating cardiac arrhythmias are therefore provided, based on the finding that "leaky" RyR2 channels, induced by FKBP12.6 deficiency in the RyR2 macromolecular complex, can trigger fatal arrhythmias.

(See Specification at p. 64, ll. 11-23; see also the materials and methods for these experiments at pp. 64-77.) Thus, the specification teaches that RyR2 channels from CPVT human patients and cardiomyoctes from FKBP12.6-deficient mice can be used as *in vitro* and *in vivo* models to investigate "therapeutic approaches for treating cardiac arrhythmias."

The specification explains the experimental results in detail, where the results show that one can use FKBP12.6-deficient mice as an animal model for arrhythmias because these mice are susceptible to exercise-induced arrhythmias. For example, the specification states: "Following exercise, when epinephrine was administered, no wild type (WT) mice had arrhythmias with this stress protocol, whereas 100% (8/8) of the FKBP12.6$^{-/-}$ mice had fatal arrhythmias consisting of a progression from a sinus rhythm (heart rate ~ 700-850 bpm) with episodes of polymorphic ventricular arrhythmias (heart rate > 1,200 bpm) to sustained ventricular arrhythmias (Fig. 9C)." (See Specification at p. 78, ll. 6-13.) The data also shows that the FKBP12.6-deficient mice had delayed after-depolarizations (pp. 78-79) and RyR2 channels with defective gating during exercise (pp. 79-80). Thus, the specification establishes that the FKBP12.6-deficient mouse can be used as a model to examine the relationship between the role of FKBP12.6 in RyR2 channel function and arrhythmia. Further, one of skill in the art would understand that such mice could be used to test candidate therapeutic agents in their ability to reduce the incidence of arrhythmia.

Experimental Set II also provides data that correlates exercise-induced sudden cardiac death and defective RyR2 gating. The specification points out the art recognized clinical phenotype of CPVT.

> "The clinical phenotype of CPVT consists of ventricular arrhythmias inducible with exercise stress testing. During exercise, patients may display a typical progression from isolated premature ventricular contractions to polymorphic ventricular tachycardia that may degenerate into ventricular fibrillation and cause sudden cardiac death (Leenhardt et al., 1995; Priori et al., 2002)."

(See Specification at p. 81, ll. 3-10.) The application discloses results of an investigation into whether there is a relationship between CPVT in humans with RyR2 function by conducting *in vitro* experiments with RyR2 forms having mutations identified in RyR2 in humans with CPVT. "To determine whether the exercise-induced arrhythmias in CPVT patients are associated with defects in SR Ca^{2+} release channel function, three mutant forms of RyR2 corresponding to known CVPT missense mutations … were expressed … To approximate the effects of exercise, which activates PKA through β-AR signaling pathways in cardiomyoctes, the single channel properties of PKA-phosphorylated WT and mutant RyR2 channels were compared in planar lipid bilayers." (See Specification at p. 81, l.12 to p. 82, l. 4.) From the experimental data, the specification concludes "[t]aken together these data show that CPVT-associated mutant RyR2 channels exhibit significantly altered single channel properties compared to WT RyR2 channels, but only after PKA phosphorylation." (See Specification at p. 83, ll. 16-19.) Thus, the experimental evidence has linked CPVT with PKA phosphorylation-dependent altered RyR2 channel function.

Because the data shows an association between disease, PKA phosphorylation, and altered RyR2 channel function, the specification then tested whether FKBP12.6 can restore normal gating to these defective RyR2 channels:

> It has previously been shown that FBKP12.6 cannot bind to PKA-phosphorylated RyR2 … Results from the present study show that FKBP12.6 also cannot bind to a mutant RyR2-S2809D that mimics constitutively PKA-phosphorylated RyR2 (Fig. 12A) … a mutant form of FKBP12.6 was generated … [which] is capable of binding to PKA-phosphorylated RyR2 and to the RyR2-S2809D mutant (Fig. 12A) … Indeed, addition of the mutant FKBP12.6-D37S restored normal (low activity) channel function to RyR2-S2809D channels (Fig. 12B). [¶] Moreover, in contrast to wild-type FKBP12.6, FKBP12.6-D37S was capable of binding to RyR2 channels isolated from exercised FKBP12.6-/- mouse hearts (Fig. 12C) and restored normal channel function (Fig. 12D). Finally, FKBP12.6-D37S, but not wild-type FKBP12.6, also bound to PKA-phosphorylated CPVT-associated RyR2 mutant channels (Fig. 12E), and restored normal channel function (Fig. 12F). … Taken together, these results suggest that partial depletion of FKBP12.6 from the RyR2 macromolecular complex, which occurs physiologically during exercise, is associated with increased RyR2 open probability, but more severe deficiency of FBP12.6 in the RyR2 complex (such as in the FKBP12.6-/- mouse or patients with

> the CPVT mutations) can result in channels with significantly increased open probability during diastole that is not observed with wild-type channels from open hearts.

(See Specification, p. 83, l. 21 to p. 84, l. 29.) As can be seen, the specification has provided considerable experimental data that establishes a connection between arrhythmias and altered RyR2 function that is based on a PKA phosphorylation / FKBP12.6 deficiency on the RyR2 channels. Contrary to the Examiner's assertions, one of ordinary skill would therefore not need to perform "undue experimentation" to establish a correlation between arrhythmia, PKA phosphorylation, FKBP12.6 binding, and RyR2 channel function.

Thus, Applicants respectfully contest the Examiner's assertion that "it would take a large quantity of experimentation to determine whether the PKA phosphorylation-induced dissociation of FKBP12.6 from RyR2 is the cause of human supraventricular tachyarrhythmia ..." As discussed above, the specification has established the utility of administering a compound that can promote FKBP12.6 binding to RyR2 receptors as a method for treating supraventricular arrhythmia. One of skill in the art would not need to conduct undue experimentation to establish a practical utility, because the specification has already provided working examples that firmly correlate ventricular arrhythmia with FKBP12.6/RyR2 channel regulation through the use of *in vitro* and *in vivo* models. Applicants would like to remind the Examiner that human testing is not the threshold requirement for utility and enablement. As stated in In re Brana, "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. § 112 ¶ 1." In re Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

The *in vitro* and *in vivo* assays that establish the relationship between arrhythmia and FKBP12.6/PKA phosphorylation-mediated RyR2 function also provide an enabling disclosure

for determining a therapeutically effective amount of JTV-519 for restoring normal gating to a type 2 ryanodine receptor (RyR2) channel. The specification explicitly informs the artisan that these assays allow for the testing of therapeutic agents:

> The present studies have implications for therapeutic approaches to cardiac arrhythmias. The elucidation of the molecular mechanisms of Ca^{2+} "leak" via RyR2 in the hearts of $FKPB12.6^{-/-}$ mice and CPVT human patients has enabled the design of specific assays to identify chemical agents that counteract the leakage of Ca^{2+} by maintaining the closed state of RyR2 channels. Strategies for enhancing closure of RyR2 channels include, but are not restricted to, reducing PKA phosphorylation of the channels, inhibiting the dissociation of FKBP12.6 from the PKA-phosphorylated channel, and mimicking the binding of FKBP12.6 to the channel with an agent that is less readily dissociated by PKA phosphorylation.

(See Specification at p. 91, ll. 1-14.) Thus, because the specification shows that JTV-519 promotes FKBP12.6 binding to PKA-phosphorylated RyR2 (see pp. 92-93), it is a strategy for enhancing the closure of RyR2 channels by inhibiting the dissociation of FKBP12.6 from PKA-phosphorylated channels. The testing of this strategy is clearly provided for by CPVT *in vitro* model and the $FKBP12.6^{-/-}$ mouse animal model. In fact, the specification informs the reader that other artisans have also demonstrated the viability of such an approach, as it "has already been demonstrated by the use of β-AR blocker drugs that inhibit PKA phosphorylation of RyR2 (Reiken et al., 2001) to prevent arrhythmias in patients with CPVT (Leenhardt et al., 1995)." (*Id.*, p. 91, ll. 28-33.)

Thus, Applicants respectfully request the Examiner to reconsider and remove the enablement rejection because it is based on an improper legal basis. There is neither a utility nor an enablement requirement that requires a therapeutic approach to be supported by actual human testing. The specification provides an enabling disclosure at least because: (1) it provides *in vitro* human evidence and *in vivo* animal model evidence that correlates PKA phosphorylation-induced dissociation of FKBP12.6 from RyR2 and human supraventricular tachyarrhythmia, which therefore provide both a practical utility and a sufficient working example of the invention, (2) it explicitly identifies JTV-519 as a therapeutic candidate and provides data that

shows JTV-519 promotes FKBP12.6 binding to PKA-phosphorylated RyR2, and (3) it teaches one of ordinary skill to how to use the *in vitro* and *in vivo* models, and that such models can be used to test the therapeutic approaches.

CONCLUSION

In view of the foregoing remarks, applicants believe that all of the Examiner's concerns have been addressed. Accordingly, applicants respectfully request reconsideration and allowance of the pending claims.

Respectfully submitted,

/Jane M. Love/
Jane M. Love, Ph.D.
Reg. No. 42,812

Date: January 23, 2008
Wilmer Cutler Pickering Hale and Dorr, LLP
399 Park Avenue
New York, New York 10022
Tel: (212) 937-7233
Fax: (212) 230-8888
jane.love@wilmerhale.com